REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1-20 have been cancelled without prejudice and replaced with new claims 21-40. The wording of the new claims are supported by the former claims. It will be noted that claim 21 has been limited to the ratio of chitosan powder to the water-insoluble polymer to "about 1:4 to about 4:1", as supported by former claim 4. Please be advised that the limitation of the ratio is for the purpose of making clearer the characteristics of the present invention, particularly because it was experimentally confirmed that the preparations of the present invention within the limited ratio of chitosan powder to the water-insoluble polymer show unexpectedly superior drug-release properties in comparison with the cited Lerner et al., as is clear from the comparative experiments shown in Dr. Shimono's Rule 132 Declaration submitted concurrently herewith.

Applicants wish to thank the Examiner for the telephonic conference held on April 14, 2006 to discuss the comparative experiments proposed by the Applicants.

As seen from the Declaration, along with the suggestion by the Examiner, the preparations of Examples 3, 4, 5, 7 and 8 of the cited Lerner et al. reference were submitted to the comparative experiments, and as the preparations of the present invention, those having various ratios of the chitosan to the water-insoluble polymer (Eudragit RS) of from 1:4 to 4:1 were tested.

(1) In Experiment 1, the release of the active ingredient was compared by using a 1st fluid as defined in Japanese Pharmacopeia (which is artificial gastric juice).

As is shown in Fig. 1, in the preparations of the cited Lerner et al., the active ingredient released almost within one hour, but on the other hand, the preparation of the present invention released the active ingredient only about 20% even after two hours.

Accordingly, it will be well understood that the preparations of the cited Lerner et al. released the active ingredient mostly in the stomach, but the preparation of the present invention shows excellent sustained release properties and can release the ingredient after passing the

stomach. Thus, the preparation of the present invention is significantly distinguished from the preparation disclosed in the cited Lerner et al., and hence the present invention would have never been suggested by the cited Lerner et al. reference.

(2) In Experiment 2, the comparison was carried out for observing the release of active ingredient by an hypothetical oral administration by using the 1st fluid (artificial gastric juice), a 2nd fluid (artificial intestinal fluid) and an aqueous solution of pH 4.0 (hypothetical fluid in the large intestine).

As seen from the experimental results, the preparation (Ref. Prepar. C) of the cited Lerner et al. swelled and disintegrated merely by the treatment with the 1st fluid (and hence could not be subjected to the test with other dissolution media) and released 60% or more of the active ingredient within 2 hours. On the other hand, the preparation (Prepar. G) of the present invention could release the active ingredient gradually through the treatment with the 1st fluid, the 2nd fluid and the solution of pH 4.0 and hence can show the desired sustained release properties.

It shall be noted that the difference between the preparation of the cited Lerner et al. and that of the present invention may be merely in the kind of the dispersed particles, calcium pectinate (in Lerner et al.) or chitosan (in the present invention) and are common in the water-insoluble polymer (i.e. Eudragit RS), nevertheless, both preparations showed significant difference in the release of the active ingredient.

This means that the preparation of the present invention using chitosan as the dispersed particles can give unexpectedly superior sustained release properties, which would have never been predicted from the cited Lerner et al.

(3) In Experiment 3, the preparations of the present invention, those having various ratios of the chitosan to the water-insoluble polymer (Eudragit RS) of from 1:4 to 4:1 were tested.

As is clear from Fig. 3, the preparations of the present invention could show the excellent sustained release properties for a long time (more than 8 hours) in the ratio of the chitosan and the water-insoluble polymer (Eudragit RS) within the ratios of 1:4 to 4:1.

(4) In Experiment 4, the pellet preparations of the present invention were subjected to the experiment in an hypothetical oral administration by using the 1st fluid (artificial gastric juice), the 2nd fluid (artificial intestinal fluid) and an aqueous solution of pH 4.0 (hypothetical fluid in the large intestine) like in Experiment 2. One of the preparations tested was an enteric coating preparation (Prepar. L).

As is seen from Fig. 4, Prepar. K of the present invention released partly the active ingredient by treating with the 1st fluid, because chitosan dissolved partly with the 1st fluid, and showed sustained release of the active ingredient by treating with the 2nd fluid (because chitosan is not dissolved at a neutral pH and hence the preparation can keep the sustained release of the active ingredient).

The enteric coating preparation (Prepar. L) did not release the active ingredient with the 1st fluid (artificial gastric juice) due to the enteric coating and did not release the ingredient either with the 2nd fluid (artificial intestinal fluid) because chitosan does not dissolve at a neutral pH range and then immediately released the active ingredient with the solution of pH 4.0 because the pellet was somewhat swelled by the treatment with the 2nd fluid and then chitosan is dissolved with an acidic solution (pH 4.0).

(5) In Experiment 5, the pellet preparations (Prepar. K and Prepar. L) of the present invention were subjected to *in vivo* test in rats, wherein the blood concentration of the active ingredient was measured.

As is seen from Fig. 5 these pellet preparation showed similar release behavior to that in Experiment 4 (*in vitro* test).

That is, Prepar. K showed sustained release properties over 12 hours and also released when passing through the stomach (during first 2 hours). On the other hand, the enteric coating preparation (Prepar. L), which is a colonic delivery preparation as claimed in original claim 1 (= new claim 22), did not release the active ingredient during passing though the stomach (first 2 hours) but after reaching the large intestine (after 5 hours), the active ingredient was rapidly released, because chitosan was decomposed faster with the bacteria in the large intestine in addition to the dissolution with an acidic solution.

As is clear from the above experimental results, the preparation of the present invention using chitosan as the dispersed particles show significantly distinguishable release properties. Such excellent properties would have never been predicted from the cited Lerner et al. reference.

Turning to the Official Action, claims 1-20 were rejected under 35 US 103 as unpatentable over Lerner et al. This ground of rejection is respectfully traversed as applied to the new claims and in view of the Declaration of Dr. Shimono.

The Examiner says that the present invention is obvious over the cited Lerner et al. '332 patent disclosing a solid formulation (preparation) comprising a water-insoluble carrier with a particulate dispersed therein, and chitosan is included in the exemplified dispersed particles.

However, chitosan used in the present invention showed significantly distinguished properties in comparison with the dispersed particles such as calcium pectinate, crospovidon, microcrystalline cellulose specifically disclosed in the cited Lerner et al. reference, when used for the solid preparation, as was experimentally proved as mentioned above.

Accordingly, it is respectfully submitted that the newly claimed invention is patentable over the cited Lerner et al. '322 patent.

In view of the foregoing, favorable reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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